

STANDPOINT

By Assoc. Prof. Kiril Nadkov Yablanski, PhD

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Member of the Scientific Jury, determined by order P-109-249 of July 30, 2019, for the defense of the dissertation work under the procedure for obtaining the educational and scientific degree "Doctor" of Dr. Tanya Kirilova Shivacheva, PhD doctoral candidate in independent form of study, in doctoral program "Internal diseases" on the topic: " *Study of clinical activity of rheumatoid arthritis in patients, treated with biological products*".

Dr. Shivacheva's work is dedicated to one of the most significant problems of modern rheumatology - rheumatoid arthritis. An essential motive for the study is that there is not always a link between the clinical, biochemical, and immunological activity of the disease, which makes it difficult to standardize methodologies for global assessment of therapeutic response. At present, there is a lack of a clear approach to assessing the therapeutic effectiveness of biological basic agents. It is unclear to what extent and how this type of therapy also affects comorbidity. The most commonly used indicators of daily activity are not sufficiently effective and objective, especially in the early stages of the disease and in the administration of some therapeutic molecules. In general, the treatment strategy of each patient (achieving remission, low or minimal disease activity, etc.) should also be tailored to the comorbidity and risk factors for the patient. Moreover, for the Bulgarian population of patients with rheumatoid arthritis undergoing biological therapy, no comprehensive assessment of aspects of the disease process has been performed.

Dr. T. Shivacheva's study was conducted at the Rheumatology Clinic of the University Hospital "St. Marina"- Varna and has a contingent of 195 patients. The dissertation is written in a volume of 190 standard typescript pages. The abstract of 58 pages is an objective reflection of the material presented in the dissertation. Two publications were presented in connection with the problem being developed.

The literature review is comprehensive, critical and in-depth and covers 292 literary sources - 2 in Cyrillic and 290 in Latin. The relevant conclusions are drawn and the outstanding issues are highlighted.

The purpose of the dissertation is clearly stated. The tasks are defined precisely and meet the stated goal. The methodology of the development is adequately structured. The contingent of patients was selected inadvertently, which ensures the objectivity of the study, ie. authenticity of the conclusions and draw conclusions and it is sufficient for statistical processing and to draw appropriate conclusions. The observed one-year treatment period with a biological drug is sufficient to evaluate its effectiveness.

A detailed and dynamic characterization of patients with rheumatoid arthritis undergoing biological therapy has been made. Traditional risk factors, as well as those derived from rheumatoid arthritis and their impact on disease activity and evolution, have been evaluated. The focus is on cardiovascular pathology, which is the most common (61.54%) and at the same time the most significant. Various models of combinations of inflammatory activity (reported by DAS 28), demographic factors, clinical and radiographic characteristics of rheumatoid arthritis, laboratory constellations, and therapeutic approach are interpreted to determine the prognostic probability of cardiovascular pathology. The probability is quantified and the opportunity to influence it in patients. Investigation and interpretation of clinical, laboratory and imaging parameters is done as they are all conditions for obtaining reliable results are met. The material is very well illustrated with 33 tables and 62 figures, which illustrates the importance of the methodologies used to track and evaluate the activity of the disease and its relation to the ongoing treatment.

Of particular practical value is the introduction of indicators representing the average disease activity of rheumatoid arthritis for a specific time period, which gives a clearer and more comprehensive characteristic of inflammatory activity and more accurate prognosis in patients. The determination of the average annual activity of arthritis and the relationship of the indicator with the probability of cardiovascular involvement was carried out for the first time in a Bulgarian population, and a contribution of original character was definitely determined.

An algorithm is proposed to initiate a personalized approach to patients' therapeutic complexes, which would improve the quality of life, prognosis, and survival of patients.

The importance of the DAS28 indicator for defining remission, low, moderate and high disease activity is interpreted, and the relationship between the DAS indicator performed by different methodologies (ESR, CRP) is evaluated.

Of great practical value is the optimization of the therapeutic concept, combining the administration of a biological drug, the addition of methotrexate, and possibly minimizing or excluding corticosteroid treatment from the therapeutic regimen and achieving DAS28 <2.67, thereby practically reducing the risk of cardiovascular pathology by about 32%.

The dissertation concludes with 6 main conclusions, which summarize the results of the observations. Outlined are 4 theoretical contributions and 3 with practically applied character, correctly defined, emphasizing the merits of the dissertation. The limitations of the study are also presented, outlining the potential for further development and complementarity of the topic.

In conclusion, it can be summarized that Dr. Tanya Shivacheva made a precise selection of the studied contingent of patients, a thorough and correctly conducted analysis of the results, as well as comparing them with the available data from the world literature so far. New researches for the Bulgarian population are presented, which together with the original methodology and the actuality of the problem give me reason to give a high appreciation of the dissertation work and propose to the Honorable members of the Scientific Jury to vote for the award of the educational and scientific degree "Doctor" Tanya Shivacheva.

09/09/2019

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Sincerely:

Assoc. Prof. Dr. K. Yablanski, PhD